

OPINION

Pharmacogenetics and geographical ancestry: implications for drug development and global health

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Abstract | Understanding and harnessing genomic variation will contribute significantly to improving the health of people in developing countries. We need to explore the nexus between pharmacogenetics, genotyping projects in developing countries, and the evolution of the pharmaceutical industry in both the developed and developing worlds. Here, we argue that, for the foreseeable future, we should focus not on boutique ‘personalized’ medicine, but on carefully defined differences between populations and ethical ways of using emerging genomics knowledge to develop drugs and improve health.

On 30 September 2004, Merck announced the worldwide withdrawal of Vioxx (rofecoxib), a multi-billion-dollar blockbuster analgesic drug, because of cardiovascular complications in those who took it for more than 18 months. It was the biggest ever withdrawal of a prescription medicine in the United States and wiped 26.8 billion US\$ off Merck’s market value that day. Was the worldwide withdrawal necessary? Or could Vioxx be resuscitated for selected populations?

Suppose that Merck had data to show that it was only individuals of north European ancestry who were affected by the adverse effects. Theoretically, Merck could still market Vioxx, with adequate warning labels to alert those people who were likely to be affected. Imagine that Vioxx was not just another analgesic but, for example, a powerful anti-retroviral or another life-saving drug that was needed by, but unaffordable to, people in developing countries. Even if the drug was safe only for Indians and Han Chinese, that would constitute a market of over 2 billion people. Merck could license Indian and Chinese companies to manufacture such a drug for their own local markets. Merck’s loss would be mitigated and pharmaceutical companies and patients in the developing world would benefit.

The completion of a good quality draft of the sequence of the euchromatic portion of

the human genome was accompanied by a commentary in *Nature* in which the future of genomics was compared to a house¹. The question we ask here is: who will live in that house? Is it only the 700 million or so people in the United States and Western Europe, or will the rest of the 6 billion people, who live mainly in the developing world, also be able to find room there?

In this article, we make two related arguments: first, that pharmacogenetics has significant relevance to the health of people in developing countries; and second, that for this benefit to be realized, we need to take into account not just differences between the genotypes of individuals, important as they are, but the differences in genotypes between different population groups.

We begin by identifying examples of how emerging knowledge about genetic and/or genomic variation is beginning to affect the pharmaceutical industry, and how pharmacogenetic strategies can be used to increase efficiency, cut costs, reduce adverse effects and increase the efficacy of drug-development pipelines. We document the trend towards using population-group genotypes in drug development and regulation, and discuss the implications of genetic differences that underlie variation in drug responses and disease susceptibility between population groups. We highlight emerging genotyping studies that are being undertaken in various regions of the developing world, and, if the vision materializes fully, the possible role of haplotype mapping in simplifying and reducing the cost of genotyping populations, potentially helping developing countries to benefit from knowledge of genetic diversity between populations. Finally, we explore how developing countries specifically will benefit from these new trends. We argue that pharmaceutical companies in developing countries will be able to harness pharmacogenetic principles and the knowledge of local genotype patterns to stimulate their industries, cut costs and generally improve the health of their populations.

Emerging industry trends

Pharmacogenetics itself is not a new discipline — it has been around for about 50 years (REF. 2) (BOX 1). What is new is that advances in genomics, particularly in methodology, have allowed us to merge pharmacogenetics with pharmacogenomics, improving our ability to identify the genetic causes of diseases and search for new drug targets. Today, several major pharmaceutical companies have teams that focus their research on the intersection between genetics, genomics and drug development, and some are already beginning to take genomic variation into account in their drug-development pipelines. Although the idea of focusing clinical trials on subgroups of individuals is not new — stratification by disease subtype has always been a goal of medical research — the use of genetics in this context is new³.

Pharmacogenetics has so far had little impact on healthcare in general, or on the pharmaceutical industry in particular. This is partly because pharmacogenetics has been thought of mainly as having boutique-style ‘personal’ applications that are unlikely to be relevant to the majority of people, particularly those in developing countries. We believe that this is about to change both with the adoption of pharmacogenetics *per se*, and because genetic differences between population groups — in addition to differences between individuals — will be taken into account. The stimulus for the adoption of these complementary emerging trends in the developed world, and particularly in the United States, will come from regulatory changes, litigation, and patient demand based on accumulating scientific evidence of the validity of the pharmacogenetics approach (see the BiDil example below). In addition, there will always be market-based incentives if entrepreneurs identify an opportunity⁴.

The role of regulation in driving pharmacogenetics is best demonstrated by the recent actions of the United States **Food and Drug Administration** (FDA). The FDA has become a proactive advocate of pharmacogenetics and pharmacogenomics⁵. A few years ago it approved alosetron hydrochloride (Lotronex, GlaxoSmithKline) for irritable bowel syndrome, but the drug was quickly withdrawn voluntarily by GlaxoSmithKline because of adverse reactions. However, because of its efficacy, patients and physicians fought for Lotronex’s return, and it was re-approved by the FDA in 2002 under restricted market terms. Now GlaxoSmithKline is studying the relationship between adverse events and genetic profiles as part of FDA-imposed post-marketing commitments⁶.

In January 2003, the FDA called for greater scrutiny of data from subpopulations, asking drug testers to use the racial categories that have been specified by the Census Bureau, to ensure consistency when evaluating potential differences in responses to drugs⁷. This is illustrated by a compelling example: a few years ago, the FDA rejected a fixed-dose combination of isosorbide dinitrate and hydralazine (now known as BiDil, NitroMed) because its efficacy in treating heart failure could not be demonstrated statistically in a clinical trial in the general population⁸. When it was tested exclusively in 1,050 self-identified African-American patients who had experienced heart failure⁹, the results of this double-blind, randomized clinical trial were so impressive that in July 2004 the trial (which was endorsed by the Association of Black Cardiologists) had to be stopped for ethical reasons; there was a significantly higher mortality rate in the placebo group than in the group given BiDil¹⁰. BiDil is now expected to be approved by the FDA in early 2005, as the first ever 'race-specific' therapy¹¹.

The role that litigation might play in driving the adoption of pharmacogenetics is illustrated by the Cassidy versus SmithKline Beecham case. This Pennsylvania class action suite alleged that SmithKline Beecham failed to warn doctors and the public that its vaccine against Lyme disease could trigger immune arthritis — an untreatable degenerative disease — in people who carry the HLA DR4+ marker, nearly a third of the United States population. Although both pre-marketing and post-marketing analyses by federal agencies have failed to confirm any increased risk from the vaccine, it was removed from the market in February 2002 as a result of plummeting sales that probably resulted from the controversy that surrounded the lawsuits¹².

A number of pharmaceutical, biotechnology and genomics companies are now turning to pharmacogenetics in their 'personalized' medicine programmes, which are most relevant for the wealthy in the developed world. Some companies are prospectively collecting and analysing samples from clinical trials to identify predictive SNPs. However, they are having difficulty in obtaining phenotypic data (for example, that relates to adverse effects) to link to information from DNA samples, and some companies are now working with the FDA to develop appropriate data-mining tools for clinical trial data. In the long term, it is perhaps more relevant to people in developing countries that pharmaceutical companies are on the lookout for genetic subgroups that could identify new targets for therapeutic drugs. Pfizer, for example, is particularly interested in hypertension-related genes in African Americans, and in diabetes-related genes that could account for the high rates of the disease in both Asian Indians and Native Americans. AstraZeneca is also looking for population differences in drug response in its clinical trials. If a drug were found to have a 'profound effect' on a particular subpopulation, AstraZeneca would label and promote it accordingly; and "if a population doesn't benefit, that could end up on the label too"¹³.

Ancestry and phenotypic differences

Studies in population genetics have revealed a great deal of genetic variation within racial or ethnic subpopulations, but also substantial variation between the five main racial groups, which are based on continental ancestry. This variation has been demonstrated in three ways¹⁴: first, ancestral tree diagrams carried out using population genetic data from indigenous groups consistently show

that *Homo sapiens* has major branches that correspond to the five main groups. Second, clusters that have recently been inferred from multi-locus genetic data and other studies coincide closely with groups that are defined by self-identified race or continental ancestry^{15,16}. Third, low-frequency alleles are more likely to be race specific. Race-specific variants are particularly common among Africans, who have greater genetic variability than other racial groups but more low-frequency alleles¹⁴. For observed phenotypic differences, self-identified race and continental ancestry often have relatively high predictive power compared to self-identified ethnicity. It is therefore likely that racial or ethnic categories will continue to be useful as long as such categorization 'explains' variation that is left unexplained by other factors¹⁵.

We must, however, be cautious as to how the results of such studies are interpreted and used¹⁷. We need a detailed understanding of each of the racial groups that are chosen for study, because the races that comprise the human species are far more heterogeneous than was previously thought. For example, individuals living in sub-Saharan rural Africa have close to 100% of what are called African alleles, whereas African Americans living in the United States show about 26% Caucasian admixture¹⁸. Some groups (for example, African-American, Caribbean and Panamanian populations) are likely to show a large degree of allelic diversity, whereas other groups (for example, sub-Saharan Africans, Inuits and Finns) are less genetically diverse. Old Amish individuals share more alleles than do individuals in other populations because they marry within their own community and as a result have a higher-than-average incidence of inborn errors of metabolism¹⁹, as do some Arab consanguineous communities. Because of founder effects and enforced segregation, Ashkenazi Jews also share a large number of alleles.

A recent meta-analysis by Ioannidis *et al.* showed that genetic variants that are associated with disease predisposition might often have similar effects across racial groups²⁰. However, in an accompanying commentary, Goldstein and Hirschhorn²¹ point out that meta-analytic studies of this type are plagued by methodological concerns, and that the results presented by Ioannidis *et al.* do not mean that people from different parts of the world will, on average, have the same genetic predispositions to disease and will respond to medicines in the same way. It is well-known that allele frequencies of functional variants often differ substantially among groups that have different geographic ancestries. For

Box 1 | Drug response variation among individuals and populations

During the past 50 years of pharmacogenetic research⁴², we have learnt that variation between individuals that is influenced by genes and other factors is relevant to the efficacy of all drugs. We now know that metabolic enzymes are affected not only by SNPs (of which the human genome contains more than 10 million), but also by other genomic variation, such as gene duplications and deletions, mutations in regulatory genes, and probably by recently-described large-scale copy number variations^{43,44}. Increasing numbers of relevant polymorphisms are being discovered. Most relevant to our discussion, we also know that the frequencies and distributions of harmful and protective polymorphisms vary greatly between human populations^{22,34,45}.

Given all of the above, it is valid to study traits that are predominantly expressed in specific populations⁴⁶. Such studies might provide a molecular basis for population differences in drug-metabolizing enzymes (for example, cytochrome P450 (REFS 47,48), sulfotransferases^{49,50} and methyltransferases⁵¹), transporters (such as ABC1 (REFS 34,52)), receptors (such as adrenergic receptors^{3,47}) and other factors that are involved in differential drug responses and disease susceptibility. Many of the population-group differences that are documented are likely to have important medical and public-health implications^{10,53–55}.

example, of 38 polymorphisms that have been associated in at least two studies with a given drug response²², two-thirds have significant allele-frequency differences between African Americans and Europeans, and many of the differences are substantial (see also BOX 1).

Genotyping in developing countries

Although it is true that many developing countries are beset by poverty, a lack of clean water, diseases that are difficult to control, illiteracy and poor governance, it can be argued that they are the ones most in need of emerging scientific and technological knowledge that might ameliorate their situations, by reducing costs and the adverse effects of drugs. At present, drugs that are tested on general populations in Europe and North America, and that are sometimes licensed on the basis of efficacy in only 30% of the subjects, are sold in developing countries without any idea of how effective or safe they are, and certainly without any regard for the local frequencies of genomic markers.

Therefore, it is not surprising that several developing countries are starting their own genotyping projects. For example, India and Thailand are both embarking on SNP-genotyping studies. Hosted by the **Genome Institute of Singapore**, an important regional initiative has recently brought scientists from China, India, Indonesia, Japan, Korea, Malaysia, Nepal, the Philippines, Singapore, Thailand and Taiwan to establish the **Human Genome Organization (HUGO) Pacific Pan-Asian SNP Initiative**, which is expected to begin in the middle of 2005. The goal of this initiative is to uncover the breadth of genetic diversity and the extent of genetic similarity within Asian populations. This information will form the basis for future studies in genomic medicine focused on Asian populations. Data from the Pan-Asian study will provide a platform for researchers in Asia to study why some populations seem predisposed to certain diseases, or do not respond to certain drugs. Cost reductions and new technologies are opening up the study to all researchers, including those with less well-developed research infrastructures.

Asia is not alone in such initiatives. Mexico has a newly-created, well-funded, federally-mandated **Institute of Genomic Medicine**, headed by Gerardo Jimenez-Sanchez²³. Genotyping the diverse Mexican populations is one of its top priorities.

Haplotype mapping

The relatively recent discovery of the haplotype structure of the human genome, and the effect that this has on SNP inheritance, could

help to simplify and reduce the cost of genotyping. When the **International HapMap project** is completed, it might be possible to use just 300,000–600,000 tag SNPs to define the most significant genetic variation. Genotyping just a handful of these carefully chosen SNPs in a chromosomal region may be enough to predict the remainder of the nearby common SNPs²⁴.

“...pharmacogenetics will probably have an impact on global health, especially on neglected infectious diseases such as malaria, tuberculosis and HIV/AIDS.”

The HapMap itself does not define the genetic diversity of subgroups, but provides a useful framework to facilitate this. It will provide a resource, but not all of the answers. A cutting-edge example of the use of haplotype mapping to understand an association between complex disease and genetics is the work of the **International Multiple Sclerosis Genetic Consortium (IMSGC)**. This example is relevant to our discussion of the value of genotyping for understanding diseases of subpopulations that have geographical ancestry in developing countries. Recognizing that multiple sclerosis (MS) is a complex genetic disorder, the IMSGC is setting out to define the most significant genetic variation that is associated with MS. By making use of the economic advantages that are provided by the emerging HapMap, as well as the falling costs of genotyping, the IMSGC expects to be able to cover the entire genome at high resolution²⁵. The consortium is also taking advantage of the observation that some groups are more prone to MS than others. It has long been known that African Americans have half the risk of developing classical MS compared with European Caucasians, and that sub-Saharan Africans rarely suffer from this condition. Providing that environmental influence is discounted, this indicates that it is the genetic contribution of Caucasians in African Americans that is responsible for the higher risk of MS in African Americans than in sub-Saharan Africans. By studying African Americans that have MS and identifying the genetic components that they have inherited from their European ancestors, the IMSGC hopes to identify regions of the genome that carry MS-susceptibility genes.

Through its value in drug development and its identification of populations that will respond favourably to a particular drug, pharmacogenetics will probably have an impact on global health, especially on neglected infectious diseases such as malaria, tuberculosis and HIV/AIDS²⁶. In the section below, we focus on specific ways in which drug development in, and for, developing countries will benefit from the recent trends discussed above.

Opportunities for developing countries

Only 16 of the 1,393 new drugs that were marketed between 1975 and 1999 were registered for diseases that predominantly affect people in developing countries, and three of those were for tuberculosis, which is not restricted to developing countries²⁷. In the future, pharmaceutical companies in the developed world will have to pay more attention to developing countries. There are at least two trends that will drive this change.

First, there is the need to gain deeper insight into the genetic basis for variable drug responses. As demand for drugs that are tailored to specific genotypes increases, pharmaceutical companies will increasingly depend on selling their products to segmented markets. Therefore, a deeper knowledge and cultivation of a wider and more extensive market outside North America and Europe will eventually be very important to them. If done correctly, this will in turn benefit people in developing countries. For pharmaceutical companies worldwide, developing countries are not only potentially huge markets for drug therapeutics but are also depositories of important human genetic diversity. Understanding this diversity is valuable because it better defines those population subgroups that will benefit more from a particular drug than others, and allows the detection of side-effects that might not be seen in populations that are mainly Caucasian. It can also help to ascertain disease predisposition. It will therefore be increasingly important to include non-Caucasian populations in clinical trials. The interest by Pfizer and AstraZeneca in the genetics of African-American and Asian-Indian subgroups living in the United States to help to identify drug targets will probably not be adequate to satisfy the need for harnessing global genetic diversity. Genotyping studies of various populations from around the world will therefore become valuable.

Second, pharmaceutical companies in developing countries are themselves poised to make significant gains on the global market²⁸. Big pharmaceutical companies can

choose to view them as rivals to be thwarted or, alternatively, as companies with which to form mutually-beneficial partnerships. For pharmaceutical companies in developing countries, pharmacogenetics might present an opportunity, especially if they learn to harness our increasing knowledge of the link between population genomic variation and health. It is true that internal economics limit the ability of many developing countries to capitalize on their genetic configurations. However, it could well be argued that, with annual *per capita* healthcare expenditures as low as 10–15 US\$, developing countries are the ones that have the greatest need of more cost-effective healthcare strategies. This will enable these countries to not waste drugs on people who will not respond or who will be harmed, and to understand the genetic basis of disease predisposition, particularly of those diseases such as HIV/AIDS, which disproportionately affect people in developing countries and impose enormous burdens on their societies.

“...with annual *per capita* healthcare expenditures as low as 10–15 US\$, developing countries are the ones that have the greatest need of more cost-effective healthcare strategies.”

Although medical exploration in developing countries can expand the genetic diversity of subjects who take part in clinical trials that lead to drug development, pharmaceutical companies that attempt to harness this valuable genomic resource will not succeed unless they work closely with the authorities in developing countries, they act ethically, they are willing to share benefits, and they form partnerships with local researchers and pharmaceutical companies. Developing countries will not cooperate if they feel that the benefits will go to others and that they are being used merely as instruments for that end. Clearly, the populations studied will also need to consent.

Drug resuscitation

In a recent review, Allen Roses described the potential useful applications of prospective efficacy and risk pharmacogenetics for drug development pipelines²⁹. He observed that

new drugs that are withdrawn for safety reasons (and, by extension, for their lack of efficacy) in Phase IIA clinical trials by commercially-driven pharmaceutical companies will probably not be used for other segments of the population, because they would no longer be protected by patents. This might be the case for big pharmaceutical companies in the developed world, but it does represent an opportunity for pharmaceutical companies in developing countries to license these compounds and develop them, both for their local populations and for other people in the developing world who are either not genetically predisposed to the adverse effects or for whom efficacy can be demonstrated to a greater extent. This idea of ‘resuscitation’ of useful drugs for different populations is also, of course, applicable to post-marketing drug withdrawals, as we proposed above for Vioxx.

Indeed, it may now be time for incentives to be developed for just such drug resuscitations, perhaps in the form of public–private partnerships. Examples of drugs that have not been developed commercially in developed countries but that are useful in developing countries include ivermectin, which has been given as a gift by Merck to patients in the developing world who are suffering from onchocerciasis (see online link [The Story of Mectizan](#)). Another example is fosmidomycin, which is a natural antibiotic that was originally developed in the 1970s for bacterial infections but that was not commercially developed by its Japanese owners, the Fujisawa Pharmaceutical Company. In the late 1990s, a potential target for fosmidomycin was identified in the partial genome sequence of the malaria parasite³⁰. Tests on mouse malaria confirmed the high level of efficacy of this drug, and fosmidomycin was rapidly tested in humans in Gabon. It has since been developed at very low cost, and is now part of the limited anti-malarial armamentarium that is at our disposal³¹. A very relevant example that is based on pharmacogenetics and geographical ancestry is BiDil. BiDil could have been discarded because it did not have demonstrable efficacy when tested on a mixed population of United States patients. However, having been tested specifically on African Americans, it has been resuscitated for that population, and is obviously now of interest to Africans who share their geographical ancestry with African Americans.

The increasing numbers of public–private partnerships that are dedicated to finding treatments for major diseases of the poor, such as the [Medicines for Malaria Venture](#), may contribute to this trend, as will the investment of 275 million US\$ that the Bill and Melinda Gates Foundation has put into

the [Grand Challenges in Global Health](#) program³². The [Institute for OneWorld Health](#), a US-based organization, aims to do something similar by identifying promising drug and vaccine candidates, developing them into safe, effective and affordable medicines, and then forming partnerships with companies and organizations in the developing world to manufacture and distribute them. The [Drugs for Neglected Diseases Initiative](#) is working along similar lines. Their models have not specifically taken into account genetic diversity, but with increasing knowledge, this might become a factor to consider in their surveys of drugs that are unlikely to be made commercial by big pharmaceutical companies.

Unexpected benefits

The compounds discovered in the research and development laboratories of developing countries may be of greater interest to big pharmaceutical companies if they can be tested in selected minority subpopulations in developed countries. For example, compounds that are found to be effective in Asian Indians in India might be of interest to United States pharmaceutical companies to market to the significant population of Asian Indians in the United States. Conversely, drugs developed by smaller companies in the developed world for their minority populations could become useful for people in developing countries: NitroMed, which developed BiDil for African-American patients, might want to partner pharmaceutical companies in developing countries to test and market the drug in sub-Saharan Africa.

The increasing numbers of drugs that will need to be tested clinically on segmented populations will put further pressure on the already grossly over-burdened capacity to perform clinical trials, particularly in the United States. The large number of clinical trials being carried out in the United States at any one time is already increasing pressure to test these drugs in developing countries³³. This will drive the trend to partner with pharmaceutical companies and organizations that carry out contract research in developing countries. A beneficial outcome of such partnerships will be that the drugs being tested might be marketed locally in developing countries, in addition to the minority population of interest in the developed country. Furthermore, the results of clinical trials of drugs developed in the developed world and then tested on patients in developing countries will be more meaningful for those populations in developing countries in whom they were tested. Conversely, the results of clinical trials carried out specifically in minority pop-

ulations, such as the trial for BiDil tested on African Americans in the United States, will also be more meaningful for patients in those developing countries from which the minorities originated.

The cost efficiency associated with the drug development strategy of prospective efficacy pharmacogenetics²⁹ will result in less-expensive drugs for patients in developing countries. When drugs are prescribed to groups who are unlikely to enjoy any benefit (and may also suffer adverse effects), the national cost of health-care is significantly higher than it need be otherwise. In Mexico, the doses of many drugs have to be altered significantly because they are either ineffective or too toxic at the levels recommended for the 'general' North American population. For example, L-asparaginase, an anti-cancer drug is given at lower doses in Mexico than in the United States to minimize toxicity (pancreatitis and/or hyperglycemia). By contrast, doses of the anti-cancer drug 6-mercaptopurine that are toxic in the United States population produce less-intense adverse effects in Mexican populations. So far, this is largely anecdotal, but the study of Mexican genomic diversity and its implications for public health is one of the priorities of the Mexican Institute of Genomic Medicine²³.

Pharmacogenetics may also feature in post-marketing surveillance. For example, some sub-Saharan African populations have a polymorphism in the *ABCB1* (ATP-binding cassette, sub-family B (MDR/TAP), member 1) gene, which encodes the multidrug transporter P-glycoprotein, such that the carriers of this polymorphism might not benefit from antiretroviral therapy³⁴. This finding might translate into the closer scrutiny and the early withdrawal of those drugs that are found to be ineffective, saving many lives and millions of dollars. This will also stimulate the search for drugs that can bypass the effects of the polymorphism.

In terms of disease susceptibility, HIV demonstrates the importance of understanding genomic variation in human patients. A subpopulation of people with a 32-base pair deletion in the chemokine (C-C motif) receptor 5 (*CCR5*) gene (the *CCR5*-Δ32 mutant allele) are sero-negative and healthy, despite repeated exposure to HIV1 infection, because the mutation prevents expression of the *CCR5* receptor on cell surfaces, which HIV uses to gain entry through mucosal surfaces. Strategies are being pursued to reduce susceptibility to HIV infection by blocking the *CCR5* receptor³⁵. Recently, United States and Swiss researchers reported that coating the vaginal surfaces of macaque monkeys with an experimental drug that binds to

CCR5 protects the monkeys against SIV (simian immunodeficiency virus) infection³⁶.

Large-scale genotyping studies will give us greater insight into the distribution and frequency of genetic variation that has important public health implications.

Conclusion

Our increasing understanding of human genomic variation, and specifically its application in pharmacogenetics, might shift our focus away from interindividual differences towards interpopulation differences. In this article, we have made three main points. First, that pharmacogenetics can be made relevant to developing countries, where it might reduce national healthcare bills. Essential drug lists in the future might have to take into account possible genomic variations between populations in developing countries. As often happens, for example with biotechnology³⁷, it is the people in developing countries, (who make up about 85% of the world's population) who could benefit the most in the long term from cutting-edge science and technology (vaccines are a good example)³⁸.

Our second point is that a deeper understanding of the genotypes of local populations with little admixture may make it possible, perhaps through the short-cuts and cost-efficiencies promised by haplotype mapping, to predict drug responses without the need to test each individual. This application will require caution and validation, but it could make an important contribution to improving drug use in economically deprived populations before the advent of personalized medicine.

Finally, there are potential opportunities for pharmaceutical companies and contract-research organizations in developing countries to capitalize on emerging trends in genotyping and their application to understanding variable drug responses and disease susceptibility. Such opportunities, if applied properly, will benefit the health of people in developing countries.

Future outlook

We have some way to go before the vision of real benefits of pharmacogenetics to developing countries materializes. Substantial knowledge gaps will need to be addressed by well-designed studies in multiple populations³⁹. There are also conceptual and technical problems that need to be resolved, and the use of population groups — at least as currently conceived in terms of race and other unsatisfactory descriptors that conflate with social constructions — is fraught with ethical and social problems that will need to be addressed with interdisciplinary research. The most satis-

factory term for population groups at present is emerging as 'geographical ancestry'; but as data accumulate, we may discover other terms for communities of common ancestry that are more scientifically accurate and that avoid social constructions completely, making it possible to move forward with less likelihood of controversy. We need to change the paradigm from 'race' to human genome variation⁴⁰.

If we are to help reduce global health

“Our increasing understanding of human genomic variation ... might shift our focus away from interindividual differences towards interpopulation differences.”

inequities we must continue to support efforts to define the nature of human variation across the world, focused primarily on medical goals³⁹. We need to formulate clear, scientifically accurate messages to educate researchers, healthcare professionals and the general public on the connections between race, ethnicity, genetics and health. For developing countries not to be left behind, to harness useful knowledge for their populations, and to avoid pitfalls, their researchers and policy-makers must participate in this important discourse as early as possible. We need an innovative global approach, such as the proposed Global Genomics Initiative⁴¹, to bring together industry, academia, non-governmental organizations and international organizations, such as the **World Health Organization**, to examine how pharmacogenetics and pharmacogenomics can best be harnessed to improve the health of people in developing countries. Pharmaceutical and biotechnology companies from both developed and developing countries should plan for the long term and consider the realities of the developing world, because that is where there will be the largest population growth, disease burden, drug demand and future markets. If markets won't work, public-private partnerships will probably be created to address the important needs of developing countries. Academics should begin empirical case studies of genotyping projects in developing countries and of early applications of pharmacogenetics in both developed and developing countries to identify good practices and avoid pitfalls.

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Competing interests statement

The authors declare no competing financial interests.

Online links

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CORRECTION

ENCODED EVIDENCE: DNA IN FORENSIC ANALYSIS

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The reference highlight for reference 120 (Hagelberg, E., Gray, L.C. & Jeffreys, A.J. Identification of the skeletal remains of a murder victim by DNA analysis. *Nature* **352**, 427–429 (1991)) incorrectly read: "The first analysis of bone samples to identify a murder victim, using mitochondrial DNA analysis." This should have read: "The first analysis of bone samples to identify a murder victim, using analysis of STRs." Jobling and Gill apologize to the authors for this error. This correction has been made to the online enhanced text and PDF version of this review.